



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US92/06415 <b>(22) International Filing Date:</b> 3 August 1992 (03.08.92) <b>(30) Priority data:</b> 750,667 27 August 1991 (27.08.91) US <b>(71) Applicant:</b> WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann Arbor, MI 48105 (US). <b>(72) Inventors:</b> SMITH, William, John ; 2425 Lancashire Drive, Ann Arbor, MI 48105 (US). WISE, Lawrence, David ; 1241 Barrister, Ann Arbor, MI 48105 (US). WUSTROW, David, Juergen ; 5101 John Holmes Road, Ann Arbor, MI 48103 (US).		<b>(74) Agents:</b> TINNEY, Francis, J.; Warner-Lambert Company, 2800 Plymouth Road, Ann Arbor, MI 48105 (US) et al.  <b>(81) Designated States:</b> AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> SUBSTITUTED THIAZEPINES AS CENTRAL NERVOUS SYSTEM AGENTS  <b>(57) Abstract</b>  Substituted thiazepines are described as well as methods for the preparation and pharmaceutical composition of same, which are useful as central nervous system agents and are particularly useful as antipsychotic and antidepressant agents as well as for treating cerebral ischemia or cerebral infarction.		

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SUBSTITUTED THIAZEPINES AS  
CENTRAL NERVOUS SYSTEM AGENTS

5

BACKGROUND OF THE INVENTION

The present invention relates to novel substituted thiazepines useful as pharmaceutical agents, to methods for their production, to  
10 pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. The novel compounds of the present invention are central nervous system agents. More particularly, the novel  
15 compounds of the present invention bind to the sigma receptor.

A number of benzomorphan opioids which selectively bind to the sigma receptor induce psychotic-like states in humans (Largent, B. L., et  
20 al, Journal of Pharmacology and Experimental Therapeutics, 238:739-748 (1986) and Tam, S. W., Proceedings of the National Academy of Sciences, USA 80:6703-6707 (1983)). Additionally, it has been reported that many known antipsychotic agents  
25 interact with the sigma receptor (Walker, M. J., et al, Pharmacological Reviews 42:355-402 (1990)). These include haloperidol, rimcazole, remoxapride, and tiospirone (Jain, A. K., et al, International Clinical Psychopharmacology 2:129-133 (1987);  
30 Guy, W., et al, Drug Development Research, 3:245-252 (1983); Moore, N. C., et al, American College of Neuropsychopharmacology, Abstract, p. 149 (1985); Lindstrom, L., et al, Psychopharmacology 86:241-243 (1985); Chouinard, G. and Annable, L.,

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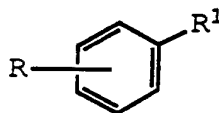
Psychopharmacology 84:282-284 (1984); and  
Chouinard, G. and Turner, L., Psychopharmacology  
Bulletin 22:267-271 (1986)).

5 We have surprisingly and unexpectedly found that  
a series of substituted thiazepines potently and  
selectively bind to the sigma receptor and are thus  
useful in the treatment of various psychotic  
disorders and in particular schizophrenia.

10 SUMMARY OF THE INVENTION

Accordingly, the present invention is a compound  
of Formula I

15



20

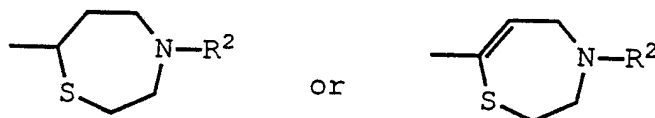
I

wherein R is  
hydrogen,  
lower alkyl,  
25 lower alkoxy,  
hydroxy,  
halogen,  
amino,  
nitro,  
30 trifluoromethyl, or  
cyano; and

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R<sup>1</sup> is

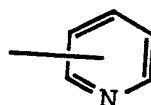
5

wherein R<sup>2</sup> is

10

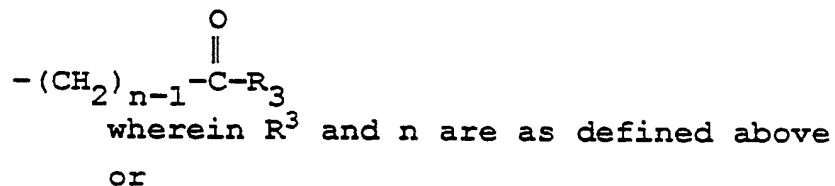
hydrogen,  
 lower alkyl,  
 $-(CH_2)_n-R^3$   
 wherein R<sup>3</sup> is

15

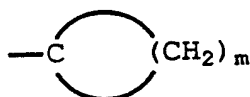


and n is an integer of 1, 2, 3, 4, or 5;

20



25



wherein m is an integer of 2, 3, 4, 5, or 6; and corresponding optical isomers thereof; or

30

a pharmaceutically acceptable acid addition salt thereof.

35

As sigma ligands, the compounds of Formula I are useful as antipsychotic agents for treating psychoses such as schizophrenia. They are also useful as antidepressants (see Rao, T.S., et al,

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Neuropharmacology 29(12):1191-1197 (1990) and Rao, T. S., et al, Neuropharmacology 29(12):1199-1204 (1990)) and as cerebroprotective agents useful in treating cerebral ischemia and cerebral infarction (see Pontecorvo, M. J., et al, Brain Research Bulletin 26:461-465 (1991) and Lobner, D. and Lipton, P., Neuroscience Letters 117:169-174 (1990)).

A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of a compound of Formula I in unit dosage form in the treatment methods mentioned above.

Finally, the present invention is directed to methods for production of a compound of Formula I.

#### DETAILED DESCRIPTION OF THE INVENTION

In the compounds of Formula I, the term "lower alkyl" means a straight or branched hydrocarbon radical having from one to six carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like.

"Lower alkoxy" is O-alkyl of from one to six carbon atoms as defined above for "lower alkyl".

"Halogen" is fluorine, chlorine, bromine, or iodine.

"Alkali metal" is a metal in Group IA of the periodic table and includes, for example, lithium, sodium, potassium, and the like.

"Alkaline-earth metal" is a metal in Group IIA of the periodic table and includes, for example, calcium, barium, strontium, magnesium, and the like.

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Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorous, and the like, as well as the salts derived from nontoxic organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanolic acids, hydroxy alkanolic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, bisulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge, S. M., et al, "Pharmaceutical Salts," Journal of Pharmaceutical Science 66:1-19 (1977)).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but

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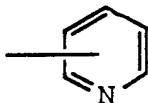
otherwise the salts are equivalent to their respective free base for purposes of the present invention.

5 Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the  
10 present invention.

Certain of the compounds of the present invention possess asymmetric carbon atoms (optical centers); the racemates as well as the individual enantiomers are intended to be encompassed within the  
15 scope of the present invention.

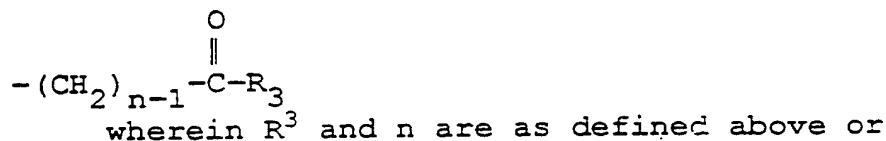
A preferred compound of Formula I is one wherein R is hydrogen,  
lower alkoxy, or  
halogen;  
20  $R^2$  is hydrogen,  
lower alkyl,  
 $-(CH_2)_n-R^3$   
wherein  $R^3$  is

25

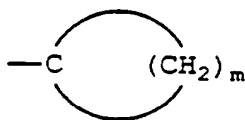


and n is an integer of 3, 4, or 5,

30



35





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wherein m is an integer of 4, 5, or 6.

Another preferred embodiment is a compound of

Formula I wherein

R is hydrogen,

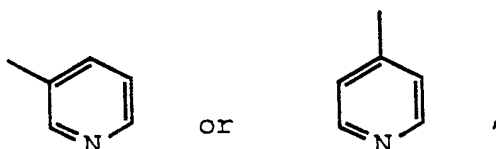
5           4-methoxy, or  
          4-chloro;

R<sup>2</sup> is hydrogen,

lower alkyl,

-(CH<sub>2</sub>)<sub>4</sub>-R<sup>3</sup>

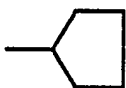
10           wherein R<sup>3</sup> is



15

$-(CH_2)_3-\overset{\overset{O}{\parallel}}{C}-R^3$  wherein R<sup>3</sup> is as defined above or

20



Particularly valuable are:

Hexahydro-7-(4-methoxyphenyl)-4-methyl-1,4-thiazepine, hydrochloride;

25       Hexahydro-7-(4-methoxyphenyl)-4-ethyl-1,4-thiazepine;

Hexahydro-7-(4-methoxyphenyl)-4-isopropyl-1,4-thiazepine, hydrochloride;

30       Hexahydro-7-(4-methoxyphenyl)-4-cyclopentyl-1,4-thiazepine, hydrochloride;

Hexahydro-7-(4-chlorophenyl)-4-methyl-1,4-thiazepine, hydrochloride;

Hexahydro-7-phenyl-4-methyl-1,4-thiazepine;

Hexahydro-7-phenyl-4-isopropyl-1,4-thiazepine;

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Hexahydro-7-(4-methoxyphenyl)-4-propyl-1,4-thiazepine;

Hexahydro-7-(4-chlorophenyl)-4-propyl-1,4-thiazepine;

5 Hexahydro-7-(4-chlorophenyl)-4-ethyl-1,4-thiazepine;

Hexahydro-7-(4-methoxyphenyl)-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine;

10 1-(3-Pyridinyl)-7-(4-methoxyphenyl)-4-(tetrahydro-1,4-thiazepin-4(2H)-yl)-1-butanone, dihydrochloride;

Hexahydro-7-(phenyl)-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine, hydrochloride;

15 Hexahydro-7-(phenyl)-4-[4-(3-pyridinyl)butyl]-1,4-thiazepine;

Hexahydro-7-(4-chlorophenyl)-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine;

2,3,4,5-Tetrahydro-7-phenyl-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine;

20 Hexahydro-7-(4-methoxyphenyl)-1,4-thiazepine; and

7-Phenyl-2,3,4,5-tetrahydro-1,4-thiazepine; and corresponding optical isomers thereof; or a pharmaceutically acceptable acid addition salt thereof.

25 The compounds of Formula I are valuable sigma ligands. The tests employed indicate that compounds of Formula I possess sigma binding activity and are thus useful in treating psychoses such as schizophrenia, as well as conditions such as depression, cerebral ischemia, and cerebral infarction. The data in the table show the inhibition of 3-PPP((+)-[<sup>3</sup>H]-3[3-hydroxyphenyl]-N-(1-propyl)piperidine; a sigma ligand) binding by

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representative compounds of Formula I, according to the method of Largent, B. L., et al, Journal of Pharmacology and Experimental Therapeutics 238:739-748 (1986). Additionally, the compounds of Formula I were tested for their ability to inhibit locomotor activity in mice according to the assay described by McLean, J. R., et al, Pharmacology, Biochemistry and Behavior 8:97-99 (1978); for their ability to inhibit contractions of electrically stimulated guinea pig ileum according to the method of Campbell, B. G., et al, Journal of Neuroscience 9:3380-3384 (1989) and Bass, P., et al, Journal of Pharmacology and Experimental Therapeutics 186:183-198 (1973). These tests further support the antipsychotic activity of the compounds of Formula I.

The above test methods are incorporated herein by reference. The data in the table show the activity of representative compounds of Formula I.

Biological Activity of Compounds of Formula I  
(Page 1 of 2)

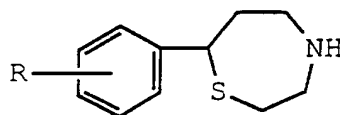
Example Number	Compound	Inhibition of Locomotor Activity in Mice ED <sub>50</sub> , mg/kg, IP	Inhibition of Contraction of Electrical Stimulation Guinea Pig Ileum IC <sub>50</sub> , μM	3-PPP Binding IC <sub>50</sub> , mM
2	Hexahydro-7-(4-methoxyphenyl)-4-methyl-1,4-thiazepine, hydrochloride		16.5	
3	Hexahydro-7-(4-methoxyphenyl)-4-ethyl-1,4-thiazepine		6.22	
4	Hexahydro-7-(4-methoxyphenyl)-4-isopropyl-1,4-thiazepine, hydrochloride		1.62	
6	Hexahydro-7-(4-chlorophenyl)-4-methyl-1,4-thiazepine, hydrochloride		121	
10	Hexahydro-7-(4-chlorophenyl)-4-propyl-1,4-thiazepine		21.31	

Biological Activity of Compounds of Formula I  
(Page 2 of 2)

Example Number	Compound	Inhibition of Locomotor Activity in Mice ED <sub>50</sub> , mg/kg, IP	Inhibition of Contraction of Electrical Stimulation Guinea Pig Ileum IC <sub>50</sub> , $\mu$ M	3-PPP Binding IC <sub>50</sub> , mM
12	Hexahydro-7-(4-methoxyphenyl)-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine	13.9	7.3	1.32
13	1-(3-Pyridinyl)-7-(4-methoxyphenyl)-4-(tetrahydro-1,4-thiazepin-4(2H)-yl)-1-butanone, dihydrochloride			9.2
14	Hexahydro-7-(phenyl)-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine, hydrochloride	13.1	13.1	6.39
15	Hexahydro-7-(phenyl)-4-[4-(3-pyridinyl)butyl]-1,4-thiazepine	17.9	4.00	2.5
16	Hexahydro-7-(4-chlorophenyl)-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine	19.0		2.62

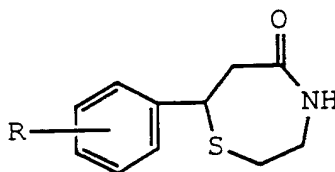
-12-

A compound of Formula Ia



Ia

wherein R is  
hydrogen,  
lower alkyl,  
lower alkoxy,  
hydroxy,  
halogen,  
amino,  
nitro,  
trifluoromethyl, or  
cyano; and corresponding optical isomers  
thereof; or a pharmaceutically acceptable acid  
addition salt thereof, may be prepared by reacting a  
compound of Formula II



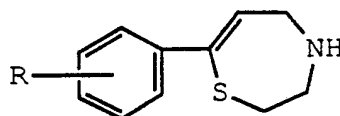
II

wherein R is as defined above with a hydride reagent  
such as, for example, aluminum hydride and the like  
in a solvent such as, for example, diethyl ether,  
tetrahydrofuran, and the like at about 0°C to about

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25°C for about 30 minutes to about 24 hours to afford  
a compound of Formula Ia. Preferably, the reaction  
is carried out with aluminum hydride in diethyl  
ether-tetrahydrofuran at about 25°C for about  
12 hours.

A compound of Formula Ib

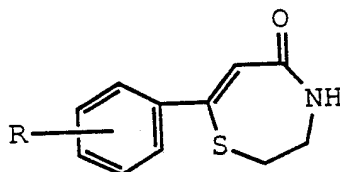


Ib

wherein R is

hydrogen,  
lower alkyl,  
lower alkoxy,  
hydroxy,  
halogen,  
amino,  
nitro,  
trifluoromethyl, or

cyano; and corresponding optical isomers  
thereof; or a pharmaceutically acceptable acid  
addition salt thereof may be prepared by reacting a  
compound of Formula III

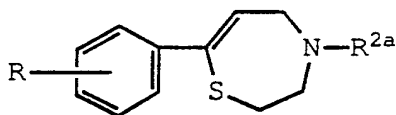


III

-14-

wherein R is as defined above with a hydride reagent such as, for example, lithium aluminum hydride and the like in a solvent such as, for example, diethyl ether and the like at about 0°C to about 25°C for about 30 minutes to about 24 hours to afford a compound of Formula Ib. Preferably, the reaction is carried out with lithium aluminum hydride in diethyl ether at about 25°C for about 12 hours.

A compound of Formula Ic



Ic

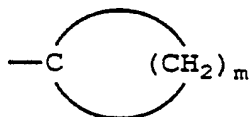
wherein R is

hydrogen,  
lower alkyl,  
lower alkoxy,  
hydroxy,  
halogen,  
amino,  
nitro,  
trifluoromethyl, or  
cyano and

R<sup>2a</sup> is lower alkyl or



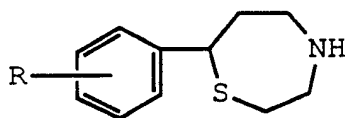
-15-



5

wherein m is an integer of 2, 3, 4, 5, or 6; and  
corresponding optical isomers thereof; or a  
pharmaceutically acceptable acid addition salt  
thereof may be prepared by reacting a compound of  
Formula Ia

10



15

Ia

wherein R is as defined above with a compound of  
Formula IV

20



IV

25

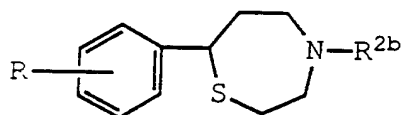
wherein  $R^{2a}$  is as defined above in the presence of  
sodium cyanoborohydride and the like and an acid such  
as, for example, acetic acid at about 25°C for about  
30 minutes to about 12 hours to afford a compound of  
Formula Ic. Preferably, the reaction is carried out  
with sodium cyanoborohydride and acetic acid at about  
25°C for about 2 hours.

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A compound of Formula Id

5



Id

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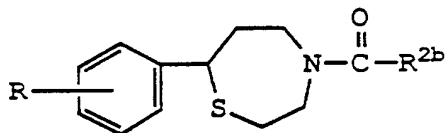
wherein R is

hydrogen,  
lower alkyl,  
lower alkoxy,  
hydroxy,  
15 halogen,  
amino,  
nitro,  
trifluoromethyl, or  
cyano, and

20

R<sup>2b</sup> is lower alkyl; and corresponding optical isomers thereof; or a pharmaceutically acceptable acid addition salt thereof may be prepared by reacting a compound of Formula V

25



30

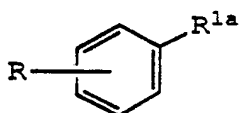
V

wherein R and R<sup>2b</sup> are as defined above with a hydride reagent such as, for example, aluminum hydride and the like in a solvent such as, for example, diethyl

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ether, tetrahydrofuran and the like at about 0°C to about 25°C for 30 minutes to about 12 hours to afford a compound of Formula Id. Preferably, the reaction is carried out with aluminum hydride in diethyl ether-tetrahydrofuran at about 25°C for about 8 hours.

A compound of Formula Ie



Ie

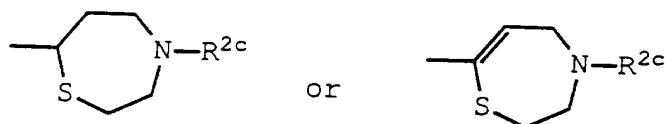
wherein R is

hydrogen,  
lower alkyl,  
lower alkoxy,  
hydroxy,  
halogen,  
amino,  
nitro,  
trifluoromethyl, or  
cyano; and

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R<sup>1a</sup> is

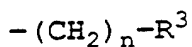
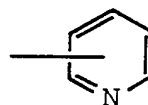
5



or

wherein R<sup>2c</sup> is lower alkyl

10

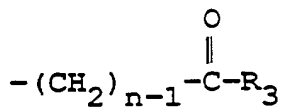
wherein R<sup>3</sup> is

and

n is an integer of 1, 2, 3, 4, or 5,

or

15

wherein R<sup>3</sup> and n are as defined above;

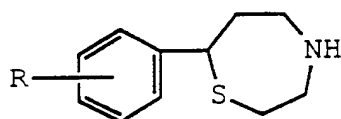
and corresponding optical isomers

20

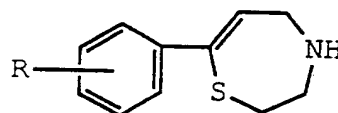
thereof; or

a pharmaceutically acceptable acid addition salt thereof may be prepared by reacting either a compound of Formula Ia or Formula Ib

25



Ia

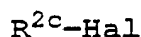


Ib

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with a compound of Formula VI

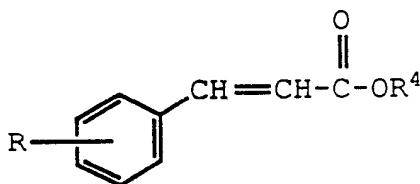
-19-



VI

5 wherein Hal is halogen and  $R^{2c}$  is as defined above in  
the presence of a base such as, for example, an  
alkali metal or alkaline earth metal carbonate or  
bicarbonate, for example, potassium bicarbonate and  
the like in a solvent such as, for example,  
10 acetonitrile and the like at about 25°C to about the  
reflux temperature of the solvent for about 1 hour to  
about 24 hours to afford a compound of Formula Ie.  
Preferably, the reaction is carried out with  
potassium bicarbonate in acetonitrile at about reflux  
15 for about 24 hours.

A compound of Formula II wherein R is as defined  
above may be prepared by reacting a compound of  
Formula VII



VII

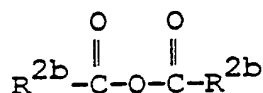
25 wherein  $R^4$  is lower alkyl and R is as defined above  
with 2-aminoethanethiol hydrochloride in the presence  
of a base such as, for example, an alkali metal or  
30 alkaline earth metal hydroxide or carbonate and the  
like, for example, sodium hydroxide in a solvent such  
as, for example, methanol and the like at about 0°C  
to about 60°C for about 1 hour to about 5 days to

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afford a compound of Formula II. Preferably, the reaction is carried out with sodium hydroxide in methanol at about 60°C for about 5 days.

5 A compound of Formula III wherein R is as defined above may be prepared by reacting a compound of Formula II wherein R is as defined above with sulfonyl chloride in a solvent such as, for example, dichloromethane and the like at about -5°C to about 25°C for about 1 hour to about 8 hours to afford a  
10 compound of Formula III. Preferably, the reaction is carried out in dichloromethane at about -5°C to about 25°C for about 8 hours.

15 A compound of Formula V wherein R and R<sup>2b</sup> are as defined above may be prepared by reacting a compound of Formula Ia with a compound of Formula VIII



20

VIII

wherein R<sup>2b</sup> is as defined above in the presence of a base such as, for example, triethylamine and the like  
25 in a solvent such as, for example, tetrahydrofuran and the like to afford a compound of Formula V. Preferably, the reaction is carried out in tetrahydrofuran.

30 Compounds of Formula IV, Formula VI, Formula VII, and Formula VIII are either known or capable of being prepared by methods known in the art.

35 Additionally, wherein a compound of Formula I is a racemic mixture, it may be further resolved into its enantiomers. Accordingly, as another aspect of

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the present invention, a compound of Formula ( $\pm$ )I may be resolved into its enantiomers by the use of conventional methodology such as, for example, optically active acids. Thus, the resulting  
5 diastereomeric salts may be separated by crystallization and then converted by conventional methodology to the optically active enantiomer (+)I or (-)I.

10 The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component either a compound of Formula I or a corresponding  
15 pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either  
20 solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers,  
25 lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided  
30 active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

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The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active



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component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

5           Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in  
10 addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

          The pharmaceutical preparation is preferably in  
15 unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such  
20 as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

25           The quantity of active component in a unit dose preparation may be varied or adjusted from 1 mg to 1000 mg preferably 10 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also  
30 contain other compatible therapeutic agents.

          In therapeutic use as antipsychotic agents, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 1 mg to about 50 mg per kilogram daily. A

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daily dose range of about 5 mg to about 25 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The following nonlimiting examples illustrate the inventors' preferred methods for preparing the compounds of the invention.

#### EXAMPLE 1

Hexahydro-7-(4-methoxyphenyl)-1,4-thiazepine, hydrochloride

Step (a): Preparation of Tetrahydro-7-(4-methoxyphenyl)-1,4-thiazepin-5-one

A mixture of 2-aminoethanethiol hydrochloride (31.0 g, 0.273 mol) and 140 mL of methanol is cooled to 0°C and treated with pulverized sodium hydroxide (12.0 g, 0.475 mol) followed by trans-methyl-4-methoxycinnamate (52.4 g, 0.273 mol). The reaction mixture is allowed to warm to room temperature and stirred for 5 days. The mixture is then heated to 60°C for 30 minutes and filtered while still warm. The methanolic solution is concentrated to ca 1/4 volume and the product is isolated by filtration (35 g).

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Step (b): Preparation of Hexahydro-7-(4-methoxyphenyl)-1,4-thiazepine

Lithium aluminum hydride (190 mL of a 1M ethereal solution) is cooled to 0°C and treated with aluminum chloride (8.44 g, 63.2 mmol) in 15 mL of diethyl ether. The resulting clear solution is stirred at 0°C for 20 minutes and then a slurry of tetrahydro-7-(4-methoxyphenyl)-1,4-thiazepin-5-one (15.0 g, 63.2 mmol) in 150 mL of tetrahydrofuran is added. The reaction is then allowed to warm to room temperature for 12 hours and is treated with 14.4 mL of water, 7.2 mL of a 10% aqueous sodium hydroxide solution and 36 mL of water. The mixture is stirred for 3 hours and filtered. The filtrate is concentrated to obtain 8.14 g of a clear oil. The oil is converted to the hydrochloride salt; mp 209-212°C.

EXAMPLE 2

Hexahydro-7-(4-methoxyphenyl)-4-methyl-1,4-thiazepine, hydrochloride

To 30 mL of acetonitrile is added hexahydro-7-(4-methoxyphenyl)-1,4-thiazepine (Example 1) (1.00 g, 4.48 mmol), an aqueous formaldehyde solution (5 mL, 57 mmol), sodium cyanoborohydride (0.30 g, 4.48 mmol) and 1 mL of acetic acid. The reaction is stirred for 2 hours and is then diluted with 40 mL of water, made basic with 15% aqueous sodium hydroxide solution and extracted with four 150 mL portions of chloroform. The combined organic layers are dried and concentrated to obtain 0.75 g of a clear oil. The oil is converted to the hydrochloride salt; mp 177°C.

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In a process analogous to Example 2 using appropriate starting materials the corresponding compounds of Formula I are prepared as follows:

5

## EXAMPLE 3

Hexahydro-7-(4-methoxyphenyl)-4-ethyl-1,4-thiazepine;  
m/z 251.

10

## EXAMPLE 4

Hexahydro-7-(4-methoxyphenyl)-4-isopropyl-1,4-  
thiazepine, hydrochloride; mp 162-163°C.

15

## EXAMPLE 5

Hexahydro-7-(4-methoxyphenyl)-4-cyclopentyl-1,4-  
thiazepine, hydrochloride; mp 196-198°C (dec).

20

## EXAMPLE 6

Hexahydro-7-(4-chlorophenyl)-4-methyl-1,4-thiazepine  
hydrochloride; mp 147-149°C (dec).

25

## EXAMPLE 7

Hexahydro-7-phenyl-4-methyl-1,4-thiazepine; m/z 207.

30

## EXAMPLE 8

Hexahydro-7-phenyl-4-isopropyl-1,4-thiazepine; m/z  
235.

35

## EXAMPLE 9

Hexahydro-7-(4-methoxyphenyl)-4-propyl-1,4-thiazepine  
Step (a): Preparation of Hexahydro-4-propionyl-7-(4-  
methoxyphenyl)-1,4-thiazepine

Hexahydro-7-(4-methoxyphenyl)-1,4-thiazepine  
(Example 1) (1.5 g, 6.72 mmol) is added to 25 mL of  
tetrahydrofuran. The reaction mixture is stirred

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while propionic anhydride (1.32 g, 10.1 mmol) and triethylamine (1.02 g, 10.1 mmol) are added. The reaction mixture is concentrated under reduced pressure and is partitioned between 1N hydrochloric acid and chloroform. The organic layer is washed with a saturated aqueous solution of sodium bicarbonate, dried with sodium sulfate, and concentrated. The reaction mixture is further purified by column chromatography on silica eluting with 98% chloroform, 2% methanol, and 0.1% anhydrous ammonia to obtain 1.10 g of a clear, colorless viscous oil which solidifies on standing; mp 134-135°C.

15     Step (b): Preparation of Hexahydro-7-(4-methoxyphenyl)-4-propyl-1,4-thiazepine

20     A solution of lithium aluminum hydride (24 mL of a 1M ethereal solution) is chilled to 0°C and treated with aluminum chloride (1.08 g, 8.00 mmol) in ca 5 mL of anhydrous diethyl ether. The clear reaction mixture is stirred for ca 20 minutes at 0°C before a solution of hexahydro-4-propionyl-7-(4-methoxyphenyl)-1,4-thiazepine (2.20 g, 7.75 mmol) is added in 10 mL of tetrahydrofuran. The reaction mixture is allowed to warm to room temperature over an 8 hour period and quenched by careful addition of 2 mL of water, followed by 1 mL of 15% aqueous sodium hydroxide solution, and finally 5 mL of water at 0°C. The reaction is stirred at room temperature for ca 25     2 hours, filtered, and the filtrate is concentrated and purified by column chromatography on silica eluting with 98% chloroform, 2% methanol, and 0.1% anhydrous ammonia, to yield 1.30 g of an oil which is converted to its hydrochloride salt; mp 117-119°C.

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In a process analogous to Example 9 using appropriate starting materials the corresponding compounds of Formula I are prepared as follows:

5

## EXAMPLE 10

Hexahydro-7-(4-chlorophenyl)-4-propyl-1,4-thiazepine;  
m/z 269.

10

## EXAMPLE 11

Hexahydro-7-(4-chlorophenyl)-4-ethyl-1,4-thiazepine;  
m/z 255.

15

## EXAMPLE 12

Hexahydro-7-(4-methoxyphenyl)-4-[4-(4-pyridinyl)-  
butyl]-1,4-thiazepine

20

To 25 mL of acetonitrile is added 1-(4-pyridinyl)-4-chlorobutane (2.00 g, 11.8 mmol), hexahydro-7-(4-methoxyphenyl)-1,4-thiazepine (Example 1) (2.63 g, 11.8 mmol), and anhydrous potassium bicarbonate (2.65 g, 47.2 mmol). The reaction mixture is heated to reflux under an atmosphere of nitrogen for 24 hours. The reaction mixture is then filtered, the filtrate concentrated, and the resulting residue is purified by column chromatography on silica eluting with 98% chloroform, 2% methanol, and 0.1% anhydrous ammonia to yield 1.58 g of the desired product; m/z 356.

25

30

In a process analogous to Example 12 using appropriate starting materials the corresponding compounds of Formula I are prepared as follows:

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## EXAMPLE 13

1-(3-Pyridinyl)-7-(4-methoxyphenyl)-4-(tetrahydro-1,4-thiazepin-4(2H)-yl)-1-butanone, dihydrochloride;  
mp 211-212°C.

5

## EXAMPLE 14

Hexahydro-7-(phenyl)-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine, hydrochloride; mp 139-140°C.

10

## EXAMPLE 15

Hexahydro-7-(phenyl)-4-[4-(3-pyridinyl)butyl]-1,4-thiazepine; m/z 326.

## EXAMPLE 16

15

Hexahydro-7-(4-chlorophenyl)-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine; mp 139-140°C.

## EXAMPLE 17

20

7-Phenyl-2,3,4,5-tetrahydro-1,4-thiazepine  
Step (a): Preparation of 3,4-Dihydro-7-phenyl-1,4-thiazepine-5(2H)-one

25

Tetrahydro-7-phenyl-1,4-thiazepin-5(2H)-one (6.23 g, 30.1 mmol) is slurried in 150 mL of dichloromethane. The reaction is cooled to -5°C and sulfuryl chloride (31.0 mL of a 1M solution in dichloromethane) is added. The reaction mixture is stirred for 3 hours at -5°C then allowed to warm to room temperature for 8 hours. The reaction mixture is concentrated to dryness under a stream of nitrogen and the residue is slurried in 50 mL of dichloromethane and stirred with a saturated solution of sodium bicarbonate. The organic layer is separated and the aqueous layer is extracted with dichloromethane. The combined organic layers are

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dried over sodium sulfate and concentrated under reduced pressure to obtain 4.13 g of a white solid; mp 148-150°C.

5

Step (b): Preparation of 7-Phenyl-2,3,4,5-tetrahydro-1,4-thiazepine

3,4-Dihydro-7-phenyl-1,4-thiazepin-5(2H)-one (3.30 g, 16.2 mmol) is added to 50 mL of absolute diethyl ether. The reaction mixture is then cooled to 0°C and lithium aluminum hydride (16.7 mL of a 1M ethereal solution) is added. The reaction mixture is then stirred overnight at room temperature and is quenched by the addition of 2.5 mL of water followed by 5 mL of 10% aqueous sodium hydroxide solution. The solids are filtered and washed with absolute ethanol. The filtrates are combined and concentrated under reduced pressure and the resulting residue is chromatographed on silica eluting with 10:1 dichloromethane:methanol to obtain 1.63 g of the product as a clear oil.

15

20

EXAMPLE 18

2,3,4,5-Tetrahydro-7-phenyl-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine

25

1-(4-Pyridyl)-4-chlorobutane is reacted with the 7-phenyl-2,3,4,5-tetrahydro-1,4-thiazepine (Example 17) using the procedure of Example 12 to give the desired product after column chromatography; m/z 324.

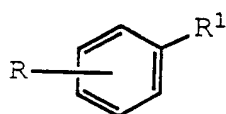
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## CLAIMS

1. A compound of Formula I

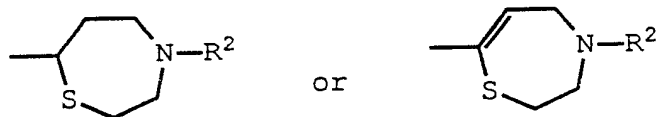


I

wherein R is

hydrogen,  
5 lower alkyl,  
lower alkoxy,  
hydroxy,  
halogen,  
amino,  
10 nitro,  
trifluoromethyl, or  
cyano; and

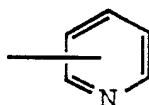
R<sup>1</sup> is



wherein R<sup>2</sup> is

15 hydrogen,  
lower alkyl,  
-(CH<sub>2</sub>)<sub>n</sub>-R<sup>3</sup>

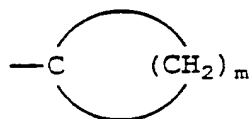
wherein R<sup>3</sup> is



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20 and n is an integer of 1, 2, 3, 4, or 5;

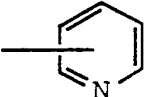
25 
$$-(\text{CH}_2)_{n-1}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{R}^3$$
 wherein  $\text{R}^3$  and n are as defined above or



wherein m is an integer of 2, 3, 4, 5, or 6; and corresponding optical isomers thereof; or  
a pharmaceutically acceptable acid addition salt thereof.

2. A compound according to Claim 1 in which  
R is hydrogen,  
lower alkoxy, or  
halogen;

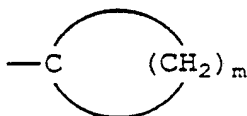
5  $\text{R}^2$  is hydrogen,  
lower alkyl,  
 $-(\text{CH}_2)_n-\text{R}^3$

wherein  $\text{R}^3$  is  and

10 n is an integer of 3, 4, or 5,

$$-(\text{CH}_2)_{n-1}-\overset{\text{O}}{\underset{\parallel}{\text{C}}}-\text{R}^3$$
 wherein  $\text{R}^3$  and n are as defined above or

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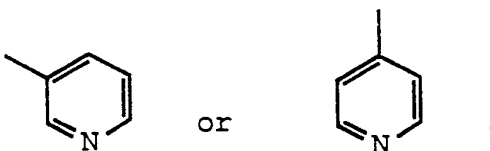
wherein m is an integer of 4, 5, or 6.

3. A compound according to Claim 2 in which

R is hydrogen,  
4-methoxy, or  
4-chloro;

5

R<sup>2</sup> is hydrogen,  
lower alkyl,  
-(CH<sub>2</sub>)<sub>4</sub>-R<sup>3</sup>  
wherein R<sup>3</sup> is



10

-(CH<sub>2</sub>)<sub>3</sub>-C(=O)-R<sup>3</sup> wherein R<sup>3</sup> is as defined  
above or

4. A compound according to Claim 3 selected from  
the group consisting of:

Hexahydro-7-(4-methoxyphenyl)-4-methyl-1,4-  
thiazepine, hydrochloride;

5

Hexahydro-7-(4-methoxyphenyl)-4-ethyl-1,4-  
thiazepine;

Hexahydro-7-(4-methoxyphenyl)-4-isopropyl-  
1,4-thiazepine, hydrochloride;

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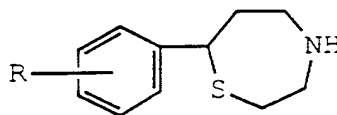
- Hexahydro-7-(4-methoxyphenyl)-4-cyclopentyl-1,4-thiazepine, hydrochloride;
- Hexahydro-7-(4-chlorophenyl)-4-methyl-1,4-thiazepine, hydrochloride;
- Hexahydro-7-phenyl-4-methyl-1,4-thiazepine;
- Hexahydro-7-phenyl-4-isopropyl-1,4-thiazepine;
- Hexahydro-7-(4-methoxyphenyl)-4-propyl-1,4-thiazepine;
- Hexahydro-7-(4-chlorophenyl)-4-propyl-1,4-thiazepine;
- Hexahydro-7-(4-chlorophenyl)-4-ethyl-1,4-thiazepine;
- Hexahydro-7-(4-methoxyphenyl)-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine;
- 1-(3-Pyridinyl)-7-(4-methoxyphenyl)-4-(tetrahydro-1,4-thiazepin-4(2H)-yl)-1-butanone, dihydrochloride;
- Hexahydro-7-(phenyl)-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine, hydrochloride;
- Hexahydro-7-(phenyl)-4-[4-(3-pyridinyl)butyl]-1,4-thiazepine;
- Hexahydro-7-(4-chlorophenyl)-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine;
- 2,3,4,5-Tetrahydro-7-phenyl-4-[4-(4-pyridinyl)butyl]-1,4-thiazepine;
- Hexahydro-7-(4-methoxyphenyl)-1,4-thiazepine; and
- 7-Phenyl-2,3,4,5-tetrahydro-1,4-thiazepine.

5. A method of treating psychoses, comprising administering to a host suffering therefrom a therapeutic effective amount of a compound according to Claim 1 in unit dosage form.

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6. A method of treating cerebral ischemia, or cerebral infarction comprising administering to a host suffering therefrom a therapeutic effective amount of a compound according to Claim 1 in unit dosage form.
7. A method of treating schizophrenia comprising administering to a host suffering therefrom a therapeutic effective amount of a compound according to Claim 1 in unit dosage form.
8. A method of treating depression comprising administering to a host suffering therefrom a therapeutic effective amount of a compound according to Claim 1 in unit dosage form.
9. A pharmaceutical composition adapted for administration as a antipsychotic, or antidepressant agent comprising a therapeutic effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.
10. A pharmaceutical composition adapted for administration as an agent for treating cerebral ischemia or cerebral infarction comprising a therapeutic effective amount of a compound according to Claim 1 in admixture with a pharmaceutically acceptable excipient, diluent or carrier.
11. A method of preparing a compound having the Formula Ia

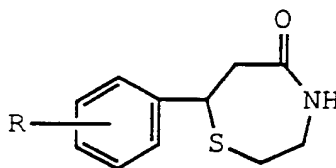
-36-



Ia

wherein R is

5           hydrogen,  
          lower alkyl,  
          lower alkoxy,  
          hydroxy,  
          halogen,  
10          amino,  
          nitro,  
          trifluoromethyl, or  
          cyano; and corresponding optical isomers  
thereof; or a pharmaceutically acceptable acid  
15          addition salt thereof, comprises reacting a  
          compound of Formula II



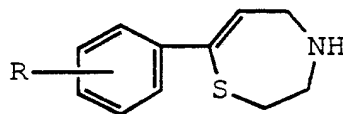
II

20          wherein R is as defined above with a hydride  
          reagent in a solvent to afford a compound of  
          Formula Ia and, if desired, converting a  
          compound of Formula Ia to a corresponding  
          pharmaceutically acceptable acid addition salt  
          by conventional means and, if so desired,  
          converting the corresponding pharmaceutically

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25 acceptable acid addition salt to a compound of  
Formula Ia by conventional means.

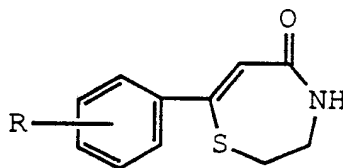
12. A method of preparing a compound having the  
Formula Ib



Ib

wherein R is

5 hydrogen,  
lower alkyl,  
lower alkoxy,  
hydroxy,  
halogen,  
10 amino,  
nitro,  
trifluoromethyl, or  
cyano; and corresponding optical isomers  
thereof; or a pharmaceutically acceptable acid  
15 addition salt thereof comprise reacting a  
compound of Formula III

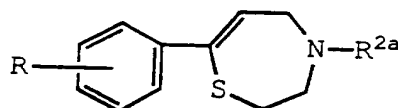


III

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wherein R is as defined above with a hydride reagent in a solvent to afford Formula Ib and, if desired, converting a compound of Formula Ib to a corresponding pharmaceutically acceptable acid addition salt by conventional means and, if so desired, converting the corresponding pharmaceutically acceptable acid addition salt to a compound of Formula Ib by conventional means.

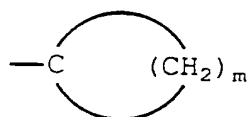
13. A method of preparing a compound having the Formula Ic



Ic

wherein R is

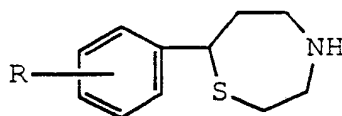
hydrogen,  
lower alkyl,  
lower alkoxy,  
hydroxy,  
halogen,  
amino,  
nitro,  
trifluoromethyl, or  
cyano and  
R<sup>2a</sup> is lower alkyl or





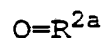
-39-

- 15 wherein m is an integer of 2, 3, 4, 5, or 6; and corresponding optical isomers thereof; or a pharmaceutically acceptable acid addition salt thereof comprises reacting a compound of Formula Ia



- 20 Ia

wherein R is as defined above with a compound of Formula IV



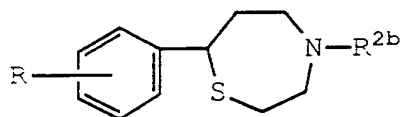
IV

- 25 wherein  $\text{R}^{2a}$  is as defined above in the presence of sodium cyanoborohydride and an acid to afford a compound of Formula Ic and, if desired, converting a compound of Formula Ic to a
- 30 corresponding pharmaceutically acceptable acid addition salt by conventional means and, if so desired, converting the corresponding pharmaceutically acceptable acid addition salt

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to a compound of Formula Ic by conventional means.

14. A method of preparing a compound having the Formula Id

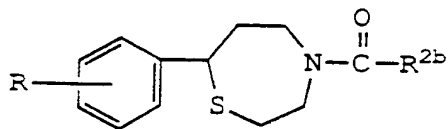


Id

wherein R is

- 5           hydrogen,  
          lower alkyl,  
          lower alkoxy,  
          hydroxy,  
          halogen,  
10          amino,  
          nitro,  
          trifluoromethyl, or  
          cyano, and

- 15          R<sup>2b</sup> is lower alkyl; and corresponding optical  
          isomers thereof; or a pharmaceutically  
          acceptable acid addition salt thereof comprises  
          reacting a compound of Formula V

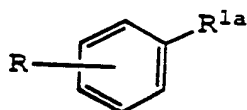


V

-41-

20 wherein R and R<sup>2b</sup> are as defined above with a  
hydride reagent in a solvent to afford a  
compound of Formula Id and, if desired,  
converting a compound of Formula Id to a  
corresponding pharmaceutically acceptable acid  
addition salt by conventional means and, if so  
25 desired, converting the corresponding  
pharmaceutically acceptable acid addition salt  
to a compound of Formula Id by conventional  
means.

15. A method of preparing a compound having the  
Formula Ie

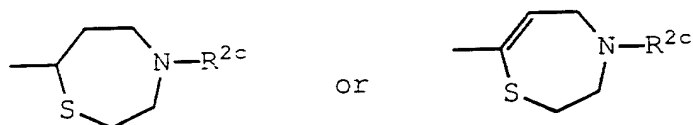


Ie

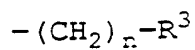
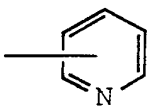
wherein R is

5           hydrogen,  
          lower alkyl,  
          lower alkoxy,  
          hydroxy,  
          halogen,  
10          amino,  
          nitro,  
          trifluoromethyl, or  
          cyano; and

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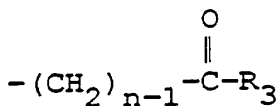
 $R^{1a}$  is

15

wherein  $R^{2c}$  is lower alkylwherein  $R^3$  is  and

$n$  is an integer of 1, 2, 3, 4,  
or 5, or

20

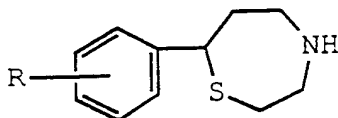
wherein  $R^3$  and  $n$  are as defined above;

and corresponding optical isomers

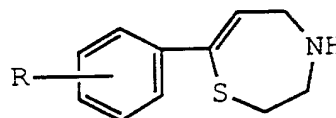
25

thereof; or

a pharmaceutically acceptable acid addition salt  
thereof comprises reacting either a compound of  
Formula Ia or Formula Ib



Ia



Ib

30

with a compound of Formula VI

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 $R^{2c}$ -Hal

VI

35 wherein Hal is halogen and  $R^{2c}$  is as defined  
above in the presence of a base and a solvent to  
afford a compound of Formula Ie and, if desired,  
converting a compound of Formula Ie to a  
corresponding pharmaceutically acceptable acid  
addition salt by conventional means and, if so  
40 desired, converting the corresponding  
pharmaceutically acceptable acid addition salt  
to a compound of Formula Ie by conventional  
means.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 92/06415

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07D281/06; C07D417/06; A61K31/55		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	C07D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
A	EP,A,0 013 749 (BASF AKTIENGESELLSCHAFT) 6 August 1980 see the whole document ---	1
A	CHEMICAL ABSTRACTS, vol. 105, no. 3, 21 July 1986, Columbus, Ohio, US; abstract no. 18233z, C.P. DOWNES ET AL. 'A comparison of the binding of sigma opioids and phencyclidine, and the interaction with antipsychotic drugs in rat brain membranes' page 59 ; see abstract & BR. J. PHARMACOL. vol. 88, no. 1, 1986, pages 231 - 237 -----	1,9,10
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
09 NOVEMBER 1992		23.11.92
International Searching Authority		Signature of Authorized Officer
EUROPEAN PATENT OFFICE		ALLARD M.S.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 92/06415

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 5-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of compounds/composition
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9206415  
SA 63430

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 09/11/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0013749	06-08-80	DE-A- 2901180	24-07-80
		AT-T- 1013	15-05-82
		AU-B- 527523	10-03-83
		AU-A- 5455780	24-07-80
		CA-A- 1134822	02-11-82
		JP-C- 1490489	07-04-89
		JP-A- 55098173	25-07-80
		JP-B- 63040789	12-08-88
US-A- 4269833	26-05-81	-----	